The Pharmacological Basis of Therapeutics

FIFTH EDITION

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respiratory depression. They are also used in the diagnosis of physical dependence on narcotic drugs and as therapeutic agents in the treatment of compulsive narcotics users, as discussed in Chapter 16. Partial agonists are also used as analgesics (*see* Table 15-3).

Treatment of Narcotic Overdosage. The dramatic effects of opioid antagonists in reversing narcotic-induced respiratory depression in the adult have already been discussed. Narcotic antagonists have also been effectively employed to decrease neonatal respiratory depression secondary to the administration of narcotics to the mother. When employed for this purpose, the antagonist may be given either to the mother shortly before delivery (preferable) or to the infant by way of the umbilical vein following delivery. The usual dose of naloxone is 0.4 or 0.8 mg for the mother; a therapeutic dose has not been established for the newborn, but 5 μg/kg has been given without adverse effects. Narcotic antagonists cannot be expected to decrease apnea of the newborn caused by trauma of delivery or other factors; they are not effective antagonists against drugs other than opioid narcotics. There is an overwhelming body of evidence showing that all known narcotics, even in reasonable therapeutic doses (*e.g.*, 10 mg of morphine, 100 mg of meperidine), produce a significant increase in the incidence of neonatal depression compared to deliveries in which no general anesthetic or narcotic is used. This increased depression is not great; however, even if the use of narcotic antagonists results in only a slight decrease in the incidence of such respiratory depression, their routine use would still appear justified whenever narcotics are administered during labor (*see* review by Eddy *et al.*, 1957). Antagonists with agonistic actions, such as nalorphine or levallorphan, should be used only when naloxone is unavailable.

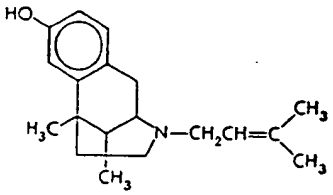
Analgesia. Pure opioid antagonists are of no value as analgesics and, because of their unpleasant side effects, agonists of the nalorphine type have not been widely used. Partial agonists of the morphine type, such as propiram, may be used in the near future. Pentazocine is discussed separately, below.

It should be emphasized that the risk of dependence is not a major limiting factor in the use of opioid analgesics for the relief of pain in acute situations. Thus, the major advantage of analgesics with low abuse liability is limited to conditions where analgesics must be given chronically or to persons whose personalities suggest a predisposition to develop psychological dependence.

PENTAZOCINE

Pentazocine is one of the many compounds synthesized as part of a deliberate effort to develop an effective analgesic with little or no abuse potential. A benzomorphan derivative, pentazocine has both agonistic actions and weak opioid antagonistic activity. It is too weak an antagonist to be classed with nalorphine, and it is also inappropriate to group it with morphine and the other opioids. The pharmacology of pentazocine has been reviewed by Brogden and associates (1973).

Chemistry. Pentazocine, a white powder soluble in acidic aqueous solutions, has the following structural formula:



Pentazocine

The analgesic and respiratory depressant activity of the racemate is due mainly to the *l* isomer.

Pharmacological Actions. Like most opioids, pentazocine exerts its major effects on the CNS and smooth muscle. The pattern of *CNS effects* is generally similar to that of the opioids, including analgesia, sedation, and respiratory depression. A dose of approximately 20 mg of the racemate or 13 mg of the *l* isomer produces the same degree of respiratory depression as does a 10-mg dose of morphine (*see* Bellville and Forrest, 1968). Increasing the dose of pentazocine beyond 30 mg does not ordinarily produce proportionate increases in respiratory depression (Engineer and Jennett, 1972). However, at doses of 60 to 90 mg, nalorphine-like dysphoric and psychotomimetic effects may occur that can be antagonized by naloxone but not by nalorphine.

The effects of pentazocine on the *gastrointestinal tract* are qualitatively similar to those of the opioids. Relatively small intramuscular doses (15 mg) significantly decrease gastric emptying time; higher doses (30 to 45 mg) increase the transit time through the intestinal tract (Danhof, 1967), but produce less elevation of biliary pressure than equianalgesic doses of morphine (Economou and Ward-McQuaid, 1971).

The *cardiovascular responses* to pentazocine differ somewhat from those seen with the opioids, in that high doses cause an increase in blood pressure and heart rate. In normal subjects, pentazocine causes a decrease in effective renal plasma flow but no decrease in glomerular filtration rate (Sigman and Elwood, 1967). In patients with coronary artery disease, pentazocine (intravenously) elevates mean aortic pressure, left ventricular end-diastolic pressure, and mean pulmonary artery pressure, and causes an increase in cardiac work (Alderman *et al.*, 1972). Pentazocine produces a rise in plasma epinephrine and norepinephrine, and this may account for its effects on blood pressure (Tammisto *et al.*, 1971).

The effects of pentazocine on *uterine contractility* do not appear to differ from those of meperidine.

Pentazocine also has weak narcotic antagonistic activity (approximately one fiftieth as potent as nalorphine). It does not antagonize the respiratory depression produced by morphine; however, when given to patients who have been receiving opioids

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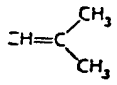

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on a regular basis, it may precipitate opioid withdrawal symptoms (Beaver *et al.*, 1966). In patients tolerant to opioids, pentazocine reduces the analgesia produced by morphine, even when clear-cut withdrawal symptoms are not produced.

Absorption, Fate, and Excretion. Pentazocine is well absorbed from the gastrointestinal tract and from subcutaneous and intramuscular sites. Plasma levels coincide closely with the onset, duration, and intensity of analgesia; peak concentrations occur 15 minutes to 1 hour after intramuscular administration and 1 to 3 hours after oral administration. Plasma half-life after intramuscular administration is about 2 hours; plasma levels are still elevated at 5 hours after oral administration (Berkowitz *et al.*, 1969).

Although some free pentazocine is excreted in the urine, the action of the drug is terminated largely by biotransformation in the liver; the metabolites, products of the oxidation of the terminal methyl groups and glucuronide conjugates, are excreted by the kidney, and approximately 60% of the total dose is eliminated within the first 24 hours. There is considerable variability between individuals in terms of rate of pentazocine metabolism, and this may account for the variability of analgesic response (*see* Brogden *et al.*, 1973). Pentazocine passes the placental barrier but to a lesser extent than does meperidine (Beckett and Taylor, 1967).

Preparations, Routes of Administration, and Dosage. *Pentazocine Lactate Injection,* N.F. (FORTRAL, TALWIN), is available in 1-, 1.5-, and 2-ml ampuls and 10-ml multiple-dose vials, each milliliter containing an amount equivalent to 30 mg of the base. *Pentazocine Hydrochloride Tablets,* N.F., for oral use contain 50 mg of the base. Pentazocine is somewhat irritating when administered subcutaneously or intramuscularly. In terms of analgesic effect, a 30- to 50-mg dose given parenterally is approximately equivalent to 10 mg of morphine. A dose of about 50 mg of oral pentazocine results in analgesia equivalent to that produced by 60 mg of codeine. In terms of peak effect, pentazocine is approximately one fourth as potent orally as parenterally; in terms of total analgesic effect, one third as potent. (*See* Beaver *et al.*, 1966, 1968; Kantor *et al.*, 1966; Morrison *et al.*, 1971.)

Side Effects, Toxicity, and Precautions. Side effects from pentazocine differ somewhat from those of opioids. The most commonly reported effect is sedation, followed by sweating, and dizziness or light-headedness; nausea also occurs, but vomiting is less common than with morphine. Nalorphine-like psychotomimetic effects such as anxiety, nightmares, weird thoughts, and hallucinations have been reported. These are not common with doses in the therapeutic range (*see* Paddock *et al.*, 1969) but are seen with increasing frequency with doses above 60 mg. The clinical picture of overdosage has not been well defined. High doses produce marked respiratory depression associated with increased blood pressure and tachycardia. The respiratory depression is antagonized by naloxone but not by nalorphine. Patients who have been receiving opioids on a regular basis may experience withdrawal symptoms when given pentazocine. After an opioid-free interval of 1 to 2 days, it is usually possible to administer pentazocine without producing such withdrawal effects.

Tolerance, Physical Dependence, and Abuse Potential. With frequent and repeated use, some tolerance develops to the analgesic and subjective effects of pentazocine; however, it is not clear if the rate of development of this tolerance is comparable to that seen with narcotic analgesics or is the same for all effects of the drug. When given intravenously or subcutaneously to postaddicts, pentazocine (40 mg) produces essentially morphine-like effects; when the dose is increased to 60 mg, the effects begin to resemble the nervousness and loss of energy produced by nalorphine. In contrast to morphine and other opioids, pentazocine does not prevent or ameliorate the morphine withdrawal syndrome when substituted in subjects physically dependent on morphine. Instead, when high doses of pentazocine are given to such subjects, its antagonistic actions, although weak, precipitate withdrawal symptoms.

Postaddicts given high doses spaced closely enough to produce continuous action on the nervous system (*e.g.*, 60 to 90 mg every 4 hours) consistently develop physical dependence that can be demonstrated by abrupt withdrawal or precipitated by naloxone but not by nalorphine. The withdrawal syndrome after chronic doses of more than 500 mg per day is similar in some respects to that seen after withdrawal of nalorphine, but it also has some of the characteristics of opioid withdrawal and, although milder, may be associated with drug-seeking behavior; that is, subjects request additional medicine to alleviate the withdrawal syndrome (Jasinski *et al.*, 1970).

In the original evaluation of the abuse potential of pentazocine, most postaddicts who were offered the opportunity to continue taking the drug elected not to do so, and few subjects in the chronic administration studies reached sufficiently high dosage to exhibit withdrawal phenomena upon abrupt discontinuation (Fraser and Rosenberg, 1964). Pentazocine was not considered to have a significant abuse potential, and it was released for general use subject to neither narcotic laws nor dangerous drug laws. Many physicians believed that the drug had no abuse potential at all and, therefore, were less than cautious in prescribing it, in permitting unlimited refilling of prescriptions, and in allowing its self-administration by ambulatory patients. Subsequently, cases of compulsive self-administration primarily of *parenteral* pentazocine were reported. Many, but not all, of these individuals previously had been dependent on opioids; most would have preferred opioids if the latter had been legal and equally available. The withdrawal symptoms seen in many of these cases included abdominal cramps, anxiety, chills, elevated temperature, vomiting, sweating, lacrimation, and drug-seeking behavior.

As the abuse potential of parenteral pentazocine became more widely appreciated, more supervision was exercised by physicians and pharmacists. The availability of the oral preparation reduced the